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Review Article

Pre-eclampsia Revisited

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Abstract

Pregnancy is state of immune tolerance and a disruption in this immunological response results in pregnancy related complications of which pre-ecalmpsia is an important and clinically relevant presentation. This is a multisystem disorder affecting 3.0 - 7.0% of nulliparous and 1 - 3% multiparas females with increased risk of morbidity and mortality.PE is a pregnancy specific disorder characterized by development of hypertension and proteinuria or hypertension with multisystem involvement. Though etiology is not clear yet it is assumed that an immunological disturbance leads to abnormal placental implantation with subsequent decrease in placental perfusion endothelial damage resulting in multisystem involvement. Despite various biomarkers available, prediction and subsequent prevention still is not possible and management focuses on hypertension control and prolongation of pregnancy till it does not cause threat to maternal or foetal outcome.

Keywords: *Preeclampsia; Immunology; Biomarkers; Outcomes*

Introduction

Hypertensive disorders of pregnancy occurs in 10%of 1st pregnancy and 6 - 8% of all pregnancies [1]. Pre-eclampsia complicates upto 10% of pregnancies in developing countries, in India maternal mortality rate due to pre-eclampsia is 8.3% [2]. Despite being the leading cause of maternal and neonatal death worldwide yet there is no effective strategies available in prevention and treatment.

Hypertension in pregnancy has generated uncertainties regarding its classification and diagnostic criteria's with centre differences in terms of adverse maternal and foetal outcomes. In 2000, the International Society for the Study of Hypertension in Pregnancy (ISSHP) identified that these uncertainties were a serious concern in terms of management and the Society appointed a committee that reviewed available classifications and endorsed and published an international recommendation for classification of these hypertensive disorders of pregnancy [3]. In 2008, the Society of Obstetricians and Gynecologists of Canada (SOGC) released revised guidelines and simplified the classification into 2 categories i.e. preexisting or gestational, with the option to add "with pre-eclampsia" to either category if additional maternal or fetal symptoms, signs, or test results support this [4]. The revised classification for hypertensive disorders in pregnancy as per ISSHP is as follows:

1. Chronic hypertension.
2. Gestational hypertension.
3. Pre-eclampsia – de novo or superimposed on chronic hypertension.
4. White coat hypertension

Latest task force recommendations of ACOG: 2013 [5] defines pre-eclampsia as hypertension and proteinuria or hypertension without proteinuria with organ involvement such as renal dysfunction, thrombocytopenia, impaired liver function, pulmonary oedma.

Timing of detection of hypertension is crucial in differentiating various types of hypertension appearing during pregnancy. At times its occurrence during second half of pregnancy without other signs of pre-eclampsia may pose difficulties in diagnosis and management.

Pre-eclampsia and gestational hypertension are characterized by the new onset of hypertension (>140 mmHg systolic or >90 mmHg diastolic) after 20 weeks gestation [6]; as such, it is important to have normal blood pressure documented either pre-pregnancy or at least in early pregnancy before there has been much pregnancy-related decrease in blood pressure. Otherwise, a normal first blood pressure measured between 16 and 20 weeks may result in a missed diagnosis of chronic hypertension.

Chronic hypertension

High blood pressure appearing before the pregnancy or values of higher blood pressures during first trimester of pregnancy. These are females who have either family history of hypertension and are often obese. One must also look for other secondary causes usually renal parenchymal disorders like reflux nephropathy, fibromuscular hyperplasia, glomerulonephritis and other endocrinal causes like primary aldosteronism.

Gestational hypertension

Development of high blood pressure after 20 weeks gestation, in the absence of accompanying proteinuria or new signs of end-organ dysfunction with normalization of blood pressures before 12 weeks post-partum failure of which it is thought to be chronic hypertension.

Severe Pre-eclampsia

A blood pressure greater than 160 mm Hg (systolic) or 110 mm Hg (diastolic) associated with proteinuria greater than or equal to 5 grams per day. Furthermore, PE is regarded as severe in the presence of multiorgan involvement including thrombocytopenia (platelet count less than 100,000/uL), pulmonary edema, or oliguria (less than 500 mL per day). In contrast, mild PE is characterized by an elevated blood pressure less than 160 mm Hg (systolic) or 120 mm Hg (diastolic) with proteinuria greater than 300 mg, but less than 5 g, per day.

The warning signs /symptoms of pre-eclampsia are

- New onset headache, visual disturbance, abdominal pain (esp. Right upper quadrant or epigastric)
- New onset proteinuria in 2nd half of pregnancy
- Fetal growth restriction
- BP elevations in pregnancy exceeding 15mm hg diastolic and 30mm hg Systolic in uncomplicated pregnancies
- Clinically evident edema or rapid weight gain: neither a specific nor a sensitive sign

Post-partum hypertension: In women with PE or superimposed PE the BP returns to normal within 48 hrs post-partum and rises again after 3 - 6 days. The exact incidence is not known. Treatment is conservative, task force suggests use of intravenous magnesium sulphate.

The disorder associated with autoimmune disorders, metabolic, vascular or renal disease which have potentially increased risk to pre-eclampsia. The table 1 shows the relative risk factors for development of pre-eclampsia. Severe pre-eclampsia can reoccur in subsequent pregnancy with incidence 25% in case of past history of severe pre-eclampsia. Previous normal pregnancy has 1% chance of pre-ecalmpsia in subsequent pregnancy.

Risk factor	Relative risk
Past history of Pre-eclampsia	7.19
Nulliparity	2.91
Family history of Pre-eclampsia	2.90
Pregestational diabetes	3.56
BP ≥ 130/80 in the first antenatal visit	1.38-2.37
APLA	9.72
BMI ≥ 26.1	2.47
CKD	Varies according to the stage
Twin pregnancy	2.93
Advanced maternal age (> 40yrs)	1.96

Time of occurrence: It mostly occurs after 34 weeks of gestation.10% occurs before 34 weeks (early onset PE) while 5% it can occur post-partum usually within 48 hours.

Clinical features

Clinically most relevant features is headache, visual disturbances, abdominal pain.

Organ specific involvement

- **Cardiovascular:** Earliest sign is hypertension which rises gradually over the gestation worsening towards term. Patient can develop oedma which is due to capillary leak presenting as rapid weight gain (>5 pounds /week) and presents as facial puffiness. The cardiac functions are largely normal with LV ejection fraction being normal yet an elevated afterload causes a decrease left ventricular performance. Sometimes there is clinical evidence of pulmonary oedma which may be due to elevated pulmonary vascular hydrostatic pressure, capillary leak, iatrogenic volume overload, CCF.

- **Renal**: This is one important organ system involved in this hypertension. Most commonly presenting as proteinuria which is usually < 5 gm/day yet nephrotic range proteinuria is also described. It is believed to be associated with podocyte injury and size and charge selectivity of glomerular filtration barrier is affected, with characteristic histological findings of glomerular endotheliosis. GFR decreases by 30 - 40%, urine is usually bland

- **Hematologic:** Thrombocytopenia is the most common hematological involvement. Microangiopathic hemolytic anemia with normal PT/APTT suggest pre-eclampsia which may be deranged in abruption/liver disease.

- **Hepatic**: Epigastric pain is the cardinal symptom resulting from stretching of the glisson's capsule sometimes they present with constant retrosternal/epigastric pain that begins at night may radiate to Right hypochondrium/back and could be the only symptom of PE. Transaminitis, subcapsular hemorrhage hepatic rupture are also seen.

- **Central nervous system:** Headache is the most prominent symptom which could be throbbing/pounding/piercing headache, visual symptoms like photopsia, Scotomata, diplopia, cortical blindness, retinal pathology can be seen. Seizures are described 1/400 in mild pre-eclampsia while 1/50 among severe pre-eclamptic women. Strokes complicate more in persistent elevated states in approx 36% of the pregnancies associated stroke.

Natural history: 25% of women with early onset PE may have rapid worsening, even eclampsia, however others gradually worsen till delivery. Delivery usually results in complete resolution of signs and symptoms of PE Symptoms usually resolve with headache settling within hours of delivery while proteinuria may take days to months and hypertension settles within 1 month can rarely persist beyond 3 months.

Pathogenesis

Usually during the first 12 weeks the decidual segments of the spiral arteries are invaded, elastic and muscular wall replaced by fibinoid walls and by 20 weeks trophoblast invades the intramyometrial segment of spiral arteries (leading from a high resistance low flow to a low resistance high flow thereby increasing in utero placental flow. However due to abnormal trophoblastic invasion in pre-eclampsia, trophoblast invasion is patchy and spiral arteries retain their muscular walls and continues as high resistance and low flow channels and poor placental perfusion.

Pathogenesis is yet not clear but there seems the central role of maternal endothelial dysfunction activating inflammatory response and accumulation of antiangiogenic factors in its causation. The current hypothesis is thought to be some immunological disturbance could have probably led to abnormal placental implantation leading to decreased placental perfusion with production of substances that activate or injure endothelial cells of the blood vessels resulting in multiple organ system involvement. The endothelial cell injury is thought to decrease levels of prostacyclin and increase thromboxane A2 levels with resultant vasospasm and endothelial cell dysfunction leading to platelet activation and micro aggregate formation somewhat like a rejection phenomenon (inadequate maternal Ab response). With compromised placental perfusion. Elevated levels of soluble fms-like tyrosine kinase 1 which is an inhibitor of vascular endothelial growth factor) with reduced levels of placental growth factor (PlGF), could be responsible to carry forward the cascade of injury and later presenting as pre-ecalmpsia. Thus, an increased sFlt-1:PlGF ratio have been observed to be associated with occurrence of preeclampsia as well as in established cases also. However, prediction of pre-eclampsia early in pregnancy with the help of these angiogenic factors have not successfully reciprocated in outcomes however its usefulness as a diagnostic tool in late pregnancy may be useful as a diagnostic aid for triaging women with singleton pregnancies and suspected preeclampsia [7-11]. There has been increasing evidences to suggest that women affected by pre-eclampsia will be at higher risk to cardiovascular disease in life [11,12]. Hence WHO has recognized the importance of pre-eclampsia by launching a programme dedicated to study and treat this problem [13].

The present literature evidences suggest that despite the defect in uteroplacental perfusion the pathophysiology revolves around the immunological disturbance leading to abnormal placentation leading to endothelial injury and multiorgan dysfunction .Thus it is thought that for a successful pregnancy there is a requirement of immune tolerance by the maternal immune system mediated through the prevalent cytokine milieu producing Th2 cells at the maternal foetal interface inhibiting Th1 response whereby helping in accepting the human foetus [20,21]. Pregnancy related complications like recurrent abortions have been associated with a tendency towards Th1 response. There is a paradigm shift from a Th2 preponderance in normal pregnancy to Th1 predominance in preeclampsia with an increase in the IL2 / IL4 and IFNg / IL4 ratios along with proinflammatory cytokines IL-6 and TNF-alpha, chemokines IL-8, IP-10, and MCP-1, and adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) as compared to normal pregnancy [22]. There has been significant co-relation between increased IP-10, MCP-1, ICAM-1, and VCAM-1 concentrations in preeclamptic patients with blood pressure values and liver and renal function parameters. There seems an increase in peripheral blood mononuclear cell production of IL-12, which induces Th1 responses, which is diminished in normal pregnant women [23].

The key role of T reg cells in situations of defective maternofoetal tolerance is been closely associated among pregnancies leading to unexplained recurrent spontaneous abortions. There is a display of low levels of Tregs in both patients own blood as well as in placenta among pregnancies especially in patients with preeclampsia. These preeclamptic patients showed a lower percentage CD4+ T cell population in peripheral blood mononuclear cells as compared to normal pregnancies and non-pregnant healthy controls. There seems lower

percentage of FoxP3+ cells in CD3+ T-cells in placental samples of pre-eclamptic women as compared to those reported in normal pregnancy subjects. Literature seems to suggest that cytotoxic T-cells may be increased at the decidua basalis in preeclampsia as the CD8+ T/CD3+ T-cells ratio was much higher than in the samples taken from healthy pregnancies. The frequency of conventional CD4+ CD25high FoxP3+ Tregs and that of nonconventional CD4+ CD25– FoxP3+ Tregs diminish in peripheral blood in preeclamptic patients as compared to healthy pregnant women. In addition, the prevalence of Th17 cells and the Th17/Treg ratio increases in peripheral blood in preeclampsia as compared with normal pregnancy [24-26].

With this background, the cytokine milieu in the serum, placental tissue and the cord blood together needs assessment regarding the pathophysiology of preeclampsia before a definite treatment can be directed against the triggering factor.

Till date no therapeutic approaches are available for treatment or prevention. Regardless of lack of existing prophylaxis and therapeutics against pre-eclampsia search for noninvasive biomarkers and sonological markers could predict the development or assist in prediction.

Prediction of Pre-eclampsia

The current status is for early detection yet there are no tests available in early pregnancy that can accurately predict pre-eclampsia. As the prevalence of Pre-eclampsia in the general population is low so a a test with high sensitivity and specificity is needed. Thus, management focuses more on adequate antenatal care. Alterations in absolute levels of angiogenic and antiangiogenic factors like VEGF, PlGF, sFlt1, and sEng may be used as biomarkers in maternal blood and urine which precede the onset of clinical preeclampsia by several weeks to months and correlate with disease severity and normalize after delivery. An increased sFlt-1:PlGF ratio have been observed to be associated with occurrence of preeclampsia. However, prediction of pre-eclampsia early in pregnancy with the help of these angiogenic factors have not successfully reciprocated in outcomes, yet its usefulness as a diagnostic tool in late pregnancy may be helpful diagnostic aid for triaging women with singleton pregnancies and suspected preeclampsia [7-11]. A combination of series of biophysical and biochemical markers that can change from as early as 1st trimester of pregnancy can help in predicting subsequent development of PE [13]. Studied biophysical markers like mean arterial blood pressure [14], uterine artery Doppler [16] and maternal cardiac output [15] are looked for prediction. Uterine artery Doppler ultrasound may detect abnormal uterine artery waveform which is presently the most promising screening procedure the classical waveforms predictive of PE in the form of either presence or absence of diastolic notching of the uterine arcuate vessels or/and a flow waveform ratios (high resistance/pulsatility index, systolic/diastolic ratios) is observed yet has high false positivity and is not routinely recommended among these studies for prediction of PE. There is some literature evidence that podocytes play a crucial role in development of pre-eclampsia and presence podocyturia at the end of 2nd Trimester would help in early prediction of pre-eclampsia. Loss of viable podocyte during pregnancy might trigger glomerular destabilization, leading to ongoing loss of podocyte and ultimately proteinuria. It is thought to be due to loss of viable podocyte during pregnancy might trigger glomerular destabilization, leading to ongoing loss of podocyte and ultimately proteinuria [17].

Prevention of pre-ecalmpsia

There are no strategically proven unequivocally effective in preventing pre-eclampsia, yet only intervention shown to have some benefit in reducing the risk of pre-eclampsia is the role of low dose aspirin [18]. The optimum dose is still not clear yet a dose of 81 mg/day is recommended around the end of first trimester to be discontinued 5 - 7 days prior to expected date of delivery. Role of calcium supplements is recommended among females with low calcium intake and not recommended beyond RDA for healthy nulliparous women.

Management of pre-eclampsia

- The objective of management revolves around prevention of complications, prevention of eclampsia and proper maternal and foetal outcomes with minimal fetal and maternal morbidity. Decision to treat weighs according to the risks and benefits to the

fetus and mother. The level of hypertension is important as severe hypertension should always be treated. Yet there is regarding over treating mild-moderate Hypertension which could be hazardous because of inhibition of fetal growth and the exposure of fetus to drug adverse effects. The need for hospitalization involves in state of worsening of hypertension and development of proteinuria in addition to existing BP. Therefore, indication for anti-hypertensives should be weighed and started in situations of severe hypertension and pre-eclampsia with severe features. One might have to start treatment early and have a lower threshold for initiating therapy in preventing adverse cerebral events. The role of less tight versus tight control of hypertension during pregnancy has found no group difference in terms of pregnancy loss, neonatal care and maternal complication but still higher frequency of maternal hypertension was observed in less tight control group [19]. A prudent approach could be considered for patient's comorbidities when deciding whether to treat mild to moderate hypertension.

- Choice of anti-hypertensive drugs- All anti-hypertensive drugs cross the placenta. No data to recommend one over the other. The decision depends on acuity of hypertension and route of administration.
- Methyl dopa has a good long-term safety profile with a mild antihypertensive effect, sedative requiring longer to act (3 - 6 hours).
- Calcium channel blockers eg-long acting Nifedipine (Not much data on Amlodipine), Verapamil, Diltiazem has good safety profile yet can cause acute precipitous fall of BP due to immediate release forms.
    - Beta blockers: Studied more frequently are labetalol, Pindolol, Metoprolol having good uteroplacental blood flow yet its safety is controversial because of premature labor, fetal growth restriction, neonatal apnea, bradycardia and hypoglycemia
    - ACE inhibitors and blockers, nitroprusside must be avoided during pregnancy.

During hypertensive emergency, intravenous hydralazine, intravenous labetalol and oral nifedipine can be used to manage such emergencies.

Physical activity: This is purely a individualized decision, among patients with stable chronic hypertension it may be of no benefit however in newly diagnosed PE in 3rd trimester it could be beneficial as per the task force recommendations.

Salt intake: A normal diet is recommended. Weight loss and low dose salt (< 100 meq /day) is not recommended in chronic hypertension (task force recommendations).

The only treatment for preeclampsia during pregnancy is to deliver the foetus. Decisions regarding delivery largely depends on the severity of the conditions in terms of potential risk to maternal as well foetal outcomes. The obstetricians in majority give the foetus as much time to mature before delivery with minimum risk to the mother. Timing of delivery depends upon the severity, duration of pregnancy and response to treatment If the pregnancy has reached term then delivery can be conducted however is it is pre –term gestation and < 34 weeks plan should be to prolong the pregnancy with conservative approach till 36 weeks however if it is 34-36 weeks the approach is uncertain. In case of fetus is < 36 weeks the obstetricians may consider options in giving the fetus more time to develop, depending on severity of the condition.

Conventionally the obstetricians consider following treatment options:

1. If the preeclampsia is mild, they could possibly wait to deliver the infant. To prevent further complications, mother may be offered to go on bed rest (to try to lower blood pressure and increase the blood flow to the placenta).
    - Careful monitoring of the mother and foetus needs to be done. Tests for the mother might include blood and urine tests to see the preeclampsia is progressing (such as tests to assess platelet counts, liver enzymes, kidney function, and urinary protein levels). Tests for the fetus might include ultrasound, heart rate monitoring, assessment of fetal growth, and amniotic fluid assessment.
    - Anticonvulsive medication, such as magnesium sulfate, might be used to prevent a seizure.

- In some cases, such as with severe preeclampsia, the woman would be required to be admitted in the hospital for closer monitoring. Treatment in the hospital might include intravenous medication to control blood pressure and prevent seizures or other complications as well as steroid injections to help speed up the development of the fetus's lungs.

2. When the woman has severe preeclampsia, the obstetricians delivers the fetus as soon as possible especially if the pregnancy has lasted more than 34 weeks. If the fetus is less than 34 weeks, then probably prescribing corticosteroids may be used to speed up the maturation of the lungs [27].
3. In some cases, obstetricians may deliver the fetus prematurely, even if that means likely complications for the infant because of the risk of severe maternal complications. The symptoms of preeclampsia usually go away within 6 weeks of delivery [26].

Conclusion

A defective maternofetal immune response may contribute to the development of pregnancy-related complications especially pre-eclampsia. There are no markers for adequate prediction for pre-eclampsia Hence prevention can be focused with use of low dose aspirin and calcium supplements among women who are deficient. Successful pregnancy with minimal maternal and foetal morbidity is the final aim. Therefore, suitable knowledge of the maternal immune response during pregnancy will enable us to understand the etiopathogenesis to elucidate prevention and to improve the treatment of these pathologies.

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